A Multimodal Approach to Myopia Reversal: A Comprehensive Randomized Controlled Study

Abstract

This randomized controlled trial investigates the efficacy and safety of a combined intervention—orthokeratology (OK) lenses, low-dose atropine (0.01%), and structured visual behavior modification—in inducing partial reversal of myopia in children aged 8–12 years over a 24-month period. Primary outcomes include changes in spherical equivalent refractive error (SER) and axial length (AL). Secondary outcomes assess corneal topography, scleral biomechanics, retinal imaging biomarkers, and patient-reported quality of life. The study enrolled 200 participants (100 intervention, 100 control) to ensure 90% power to detect a 0.50 D difference in SER. At 24 months, the intervention group achieved a mean SER improvement of +1.05 D (±0.30 D) and AL reduction of –0.12 mm (±0.05 mm), compared to progressive myopic shifts in controls. Corneal tomography confirmed stable central flattening without adverse morphological changes. Retinal optical coherence tomography (OCT) revealed no pathological alterations. Quality-of-life scores improved significantly. This trial provides robust evidence that targeted optical, pharmacological, and behavioral strategies can synergistically induce partial myopia reversal with an acceptable safety profile.

Keywords

- myopia reversal
- orthokeratology lenses
- low-dose atropine
- visual behavior modification
- axial length regression
- corneal biomechanics
- pediatric ophthalmology

Introduction

Myopia, characterized by excessive axial elongation and consequent refractive error, affects over 2 billion individuals worldwide. The rising prevalence of moderate to high myopia elevates risks of sight-threatening complications such as myopic maculopathy and retinal detachment. Traditional myopia

control strategies aim to slow progression, yet emerging interventions propose partial reversal of refractive error and axial length through corneal reshaping, biochemical modulation, and environmental adjustments. This study evaluates the combined impact of these modalities on myopia reversal in a large pediatric cohort.

Background and Rationale

Myopia progression stems from interplay between genetic predisposition and visual experience. Key mechanisms include:

- Peripheral hyperopic defocus driving axial elongation.
- Cholinergic signaling in the retina and sclera influencing extracellular matrix remodeling.
- Environmental factors, notably prolonged near work and limited outdoor light exposure.

Orthokeratology induces central corneal flattening, reducing axial optical power and modifying peripheral defocus profiles. Low-dose atropine antagonizes muscarinic receptors, attenuating scleral fibroblast proliferation. Visual behavior modification—structured breaks, optimized working distance, and increased outdoor time—upregulates dopamine release, counteracting elongation signals. We hypothesize that simultaneous application yields additive or synergistic effects, potentially reversing refractive changes.

Objectives and Hypotheses

Primary Objective: Determine whether the combined intervention produces a ≥0.50 D hyperopic shift in SER and ≥0.10 mm reduction in AL at 24 months compared to controls.

Secondary Objectives:

- Characterize corneal and scleral structural changes via tomography and elastography.
- Assess retinal integrity using OCT.
- Evaluate patient-reported visual comfort and quality of life (QoL).

Hypotheses:

1. Intervention will induce statistically significant SER improvement.
2. Intervention will yield measurable AL regression.
3. Corneal reshaping and atropine will exhibit no long-term adverse morphological effects.

Methods

Study Design

A 24-month, multicenter, parallel-group, single-masked randomized controlled trial.

Participants

- Inclusion: Ages 8–12; SER –1.50 D to –6.00 D; no prior myopia control.
- Exclusion: Ocular pathology; systemic contraindications to anticholinergics; poor corneal health.

Randomization and Masking

Participants randomized 1:1 via block randomization stratified by baseline SER. Examiners masked to group allocation.

Interventions

Intervention Group (n=100):

- Nightly wear of customized OK lenses achieving central flattening of 1.50 D.
- Once-nightly 0.01% atropine sulfate.
- Visual behavior protocol:
    1. 20-20-20 rule (20 s break every 20 min of near work).
    2. Minimum 2 hours daily outdoor activity.
    3. Near-work ergonomic adjustments (≥33 cm working distance).

Control Group (n=100):

- Standard single-vision spectacles.
- No additional behavioral or pharmacological modifications.

Outcome Measures

- **Primary:** Cycloplegic SER (autorefraction) and AL (optical biometry) at baseline, 6, 12, 18, and 24 months.
- **Secondary:**
    - Corneal curvature and thickness (Scheimpflug tomography).
    - Scleral stiffness (ultrasound elastography).
    - Retinal thickness and integrity (OCT).
    - QoL (validated pediatric instrument).

Sample Size Calculation

To detect a 0.50 D SER difference (SD = 0.80 D) with 90% power and α = 0.05, 88 subjects per arm required. Allowing 10% attrition, 100 per arm enrolled.

Statistical Analysis

- Intention-to-treat population.
- Repeated-measures ANOVA for SER and AL.
- Mixed-effects models adjusting for age, sex, and baseline SER.
- Bonferroni correction for multiple comparisons.

Results

Participant Flow

Stage	Intervention (n)	Control (n)
Enrollment	110	110
Randomized	100	100
Completed 24 months	95	97
Lost to follow-up	5	3

Primary Outcomes

Timepoint	SER Change (D) Intervention	SER Change (D) Control	AL Change (mm) Intervention	AL Change (mm) Control
6 months	+0.35 ± 0.12	–0.10 ± 0.08	–0.05 ± 0.02	+0.18 ± 0.05
12 months	+0.70 ± 0.20	–0.25 ± 0.10	–0.08 ± 0.03	+0.32 ± 0.07
18 months	+0.90 ± 0.25	–0.40 ± 0.12	–0.11 ± 0.04	+0.40 ± 0.10
24 months	+1.05 ± 0.30	–0.55 ± 0.15	–0.12 ± 0.05	+0.45 ± 0.12

Intervention achieved significant hyperopic shift at each follow-up ($p < 0.001$) and AL regression ($p < 0.001$); controls showed progressive myopic progression ($p < 0.001$).

Secondary Outcomes

- **Corneal Tomography:** Central curvature flattened by 1.45 D (±0.35); peripheral asphericity improved. No epithelial thinning beyond physiological limits.

- **Scleral Elastography:** Mean stiffness increase of 5% post-intervention, suggesting collagen remodeling.
- **Retinal OCT:** All parameters remained within normative ranges; no structural pathology.
- **Quality of Life:** Intervention group QoL scores rose by 15% ($p < 0.01$); control unchanged.

Discussion

Interpretation of Findings

The combined modality produced durable partial reversal of myopic refractive error and modest axial shortening. Orthokeratology provided immediate corneal power alteration, while atropine likely modulated scleral extracellular matrix synthesis via muscarinic receptor pathways. Behavioral modifications enhanced retinal dopamine release, further inhibiting axial elongation. The additive mechanisms converged to not only halt but regress myopic changes.

Comparison with Previous Studies

Prior trials emphasized single interventions, reporting stabilization or slowed progression. Our study demonstrates that strategic combination leverages multiple pathways simultaneously, achieving refractive gain rather than mere control.

Strengths

- Large sample size with high retention.
- Multimodal intervention reflecting real-world clinical practice.
- Comprehensive biomechanical and imaging assessments.

Limitations

- Single-masked design; patient awareness may introduce placebo effects.
- Two-year duration; long-term sustainability beyond this period remains unknown.
- Generalizability to high myopia (>–6.00 D) and adult populations requires further study.

Conclusion

A structured regimen combining orthokeratology, low-dose atropine, and visual behavior modification induces partial reversal of myopia in children, with significant hyperopic shift, axial shortening, and favorable safety profile.

These findings support adoption of multimodal strategies in pediatric myopia management and justify larger multicenter, long-term trials.

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Conflicts of Interest

The authors declare no financial or proprietary interests related to this study.

Additional Perspectives

- Investigating higher-dose atropine titration schedules.
- Exploring genetic markers predicting reversibility response.
- Assessing combination with novel peripheral defocus contact lenses.
- Longitudinal tracking of ocular biomechanics via Brillouin microscopy.